Remarks

Claims 1-16 were pending in the subject application. By this Amendment, claims 1, 9, and 13 have been amended. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Claims 10-12 remain pending but withdrawn from consideration. Accordingly, claims 1-9 and 13-16 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

At the outset, Applicants wish to thank Examiner Harris for the productive interview conducted with their representative, Chalin Smith, on November 1, 2005. Applicants submit that the instant amendment is commensurate with the comments set forth during the personal interview.

As discussed during the interview, to expedite prosecution, Applicants have amended the specification to incorporate the prior art definition of the cancer-specifically expressed mutant MK lacking the N-terminal domain, a definition previously incorporated by reference to the publication to Kaname T. *et al.* (Biochem. Biophys. Res. Commun., 219: 256-260, 1996) cited in the originally filed specification at p. 5, line 4. The inserted text is copied from p. 258 of the Kaname T *et al.* publication, specifically from the first paragraph under the "DISCUSSION" heading. In accordance with 37 C.F.R. §1.57(f), Applicants submit that the material being inserted into the specification is the material previously incorporated by reference. Although the Kaname T. *et al.* reference has been cited previously and thus is already of record, Applicants nevertheless include herewith a supplemental courtesy copy of this publication as Appendix A. Note, the originally filed application expressly states at p. 12, lines 3-4, that "All prior art publications cited in this description are incorporated herein by reference." As noted in M.P.E.P. §2163.07, information incorporated by reference is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. Accordingly, Applicants respectfully submit that the instant amendment to the specification is proper and does not introduce new matter.

To further expedite prosecution, Applicants have amended the claims as follows:

- Claims 1, 9, and 13 have been amended to refer to "full-length human midkine or a truncated form thereof that lacks the entire N-terminal domain disposed between Asp26 and Gly81"; and
- Claims 1 and 9 have been amended to affirmatively recite "diagnosing the presence of early cancer, defined as stage 0 or stage I of the TNM classification, when the comparison of (b) indicates that the measured level is elevated as compared to the control level".

Support for these amendments is found in the specification as originally filed and amended herein, particularly at p. 3, lines 1-4 ("a screening diagnosis of early cancer was made possible through the highly sensitive detection of MK levels appearing in the body fluid of patients at an early stage of various cancers"), p. 3, lines 9-10 ("the present invention relates to . . . a method for diagnosing early cancer") and p. 4, line 36 to p. 5, line 7 ("the term "MK" includes a full-length MK protein, and a . . . truncated MK lacking the N-domain that is expressed cancer-specifically. (Kaname T. et al.: Biochem. Biophys. Res. Commun., 219: 256-260, 1996). . .the peptide portion between Asp26 and Gly 81 was deleted in the truncated form."). Accordingly, Applicants respectfully submit that no new matter has been added.

Turning to the Office Action of June 3, 2005:

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-9 and 13-16 stand rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner finds the recitation of "human midkine" to encompass a genus of proteins, noting that the definition of midkine in the specification mentions fragments and mutants. According to the Examiner, this genus encompasses "midkine molecules that vary widely in structure and function."

Applicants respectfully disagree. Nevertheless, to expedite prosecution, Applicants have amended claims 1, 9, and 13 to refer to "full-length human midkine or a truncated form thereof that lacks the entire N-terminal domain disposed between Asp26 and Gly81". The DNA sequence

encoding the human full-length MK is well known, as demonstrated by U.S. Patent No: 5,461,029 referenced in the specification. The truncated form, devoid of the N-terminally located domain, is also well known in the prior art and described in the Kaname T. *et al.* reference discussed above as well as Aridome, K. *et al.*, British J. of Cancer, 78(4): 472-477 (1998). Courtesy copies of each reference are provided herewith, labeled Appendices A and B, respectively.

Thus, Applicants respectfully submit that the claims as amended herein do not encompass a "genus of midkines molecules" that vary widely in structure and function. Accordingly, Applicants respectfully submit that the originally filed specification provides sufficient written description of the invention of the pending claims so as to demonstrate possession thereof. As such, Applicants request that the written description rejection be reconsidered and withdrawn.

Claims 1-9 and 13-16 stand further rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method involving the step of measuring the level of full-length human midkine protein in a biological sample, does not reasonably provide enablement for methods involving measuring the level of midkine mutants or fragments.

Applicants respectfully submit that the amendments presented herein render this rejection moot. Specifically, the claims as amended do not encompass "arbitrary" mutants and fragments of MK. Applicants and other researchers have clearly demonstrated that the midkines encompassed by the instant claims – namely, full-length human midkine and truncated human midkine lacking the N-terminal domain – are both expressed in a cancer-specific manner such that they may be readily adapted for use in the detection of early cancer and the assessment of cancer prognosis, according to the methods presently claimed. See, for example, the Test Examples 1-9 of the instant specification (pages 15-21) as well as the Kaname *et al.* and Aridome *et al.* references discussed above. Accordingly, Applicants respectfully submit that one skilled in the art could readily perform the methods of the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Thus, Applicants respectfully submit that the scope of the claims is commensurate with the scope of the enabling disclosure. Accordingly, Applicants request that the enablement rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. §§102 & 103

Song et al.:

Claims 1-9, 13, and 14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Song *et al.* (Biomedical Research, 1997). According to the Examiner, Song *et al.* disclose a method for measuring a human midkine protein in the sera of patients with early stage gastric, hepatocellular and lung cancer, wherein detection and measurement of MK was conducted using an enzyme linked immunoassay using a pair of antibodies.

The Examiner has acknowledged that the Song *et al.* reference fails to expressly indicate the stage of the carcinomas assayed. Accordingly, any assertion of anticipation must necessarily be a result of inherency, *i.e.*, asserting that the Song *et al.* reference ***inherently*** discloses the screening of early cancer, defined in the instant claims as cancer of TNM stage 0 or stage I. Further to this suggestion, the Examiner states that "it is reasonable to regard these cancers [*i.e.*, those tested by Song *et al.*] as early stage cancers as defined by Applicants because as noted in the Table found on page 376 of Song these cancers have no lymph node metastasis, which is a reflection of being stage 0 or stage I cancer." However, inherency may not be established by probabilities and possibilities, no matter how reasonable. Rather, as noted previously, for a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to *prove its existence* in the prior art. The mere fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). In other words, the missing element or function must *necessarily* result from the prior art reference. Importantly, the burden of proof is on the Examiner to provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic or missing element ***necessarily flows*** from the teachings of the prior art. See *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI, 1990) (emphasis original). This the Examiner has not done.

In this case, the Examiner appears to have ignored the fact that "a cancer that has not metastasized is not necessarily an 'early cancer' as that term is defined in the instant specification (*i.e.*, a cancer categorized as stage 0 or stage I of the TNM classification)" (see declaration of Dr. Kodamatsu, point 6). Nevertheless, in an effort to further clarify this point, Applicants submit

herewith a summary chart (labeled Appendix C) and supporting documents (labeled Appendices D through M) demonstrating that the absence of lymph node metastasis is not a characteristic exclusive to early cancer. In fact, in each and every type of cancer assayed by Song *et al.*, the absence of lymph node metastasis (designated under the TNM classification as "N0") can be characteristic of Stage II cancer, and, in some cases even extends to Stage III (see, for example, gastric carcinoma, hepatocellular carcinoma, bile duct and gallbladder carcinoma, and thyroid carcinoma). Accordingly, given the limited data provided, it is impossible to conclusively determine the stage of the cancer samples assayed by Song *et al.*, much less prove with sufficient clarity that any of the samples were stage 0 or stage I, as the pending claims require.

Furthermore, as Dr. Kodamatsu's declaration evidences, at the time of invention, "no one thought that samples derived from early stage cancer patients would yield positive results". Not only were serum-based diagnostic markers for early cancer "virtually non-existent" but "it was the general view that finding markers for early cancer was virtually impossible." (Kodamatsu, point 7). Given the fact that there is no direct relationship between a cancer not metastasizing to the lymph nodes and that cancer being an early cancer and the fact that, at the time of invention, there were virtually no serum-based protein markers for early cancer, it does not ***necessarily flow*** that the patients studied in the Song *et al.* reference were afflicted with early cancer, namely a cancer that is TNM stage 0 or stage I as required by the instant claims. Accordingly, as the Song *et al.* reference fails to disclose, either expressly or inherently, an element of the claim (*i.e.*, early cancer), it cannot anticipate the claims as amended herein.

At page 9 of the outstanding Office Action, the Examiner states that "Song continues to anticipate the claimed invention . . . because Applicants' claim 1, part b, implicitly notes 'wherein an elevated measured level as compared to the control indicates the presence of early cancer'". The Examiner then asserts that the instant claims "read on methods absolute in the contrast of elevated midkine within samples compared to the control, which is within the scope of the claims." According to the Examiner, given the description established in the claims and Song's data findings (in which normal human serum was shown to contain undetectable or low levels of MK whereas serum levels of MK in patients with hepatocellular carcinoma were markedly increased), "Song's method was conducted with early cancer patients and thus anticipate the claims."

Applicants are a bit confused by the Examiner's logic and respectfully disagree with her conclusions, which appear to be non-sequitur. For example, it appears that the Examiner has ignored the direction of the preamble, which clearly breathes life and meaning into the claim, and, therefore, should be accorded patentable weight. Nevertheless, to expedite prosecution, Applicants have amended method claims 1 and 9 to affirmatively recite "diagnosing the presence of" early cancer. While it may be argued that Song *et al.* disclose the steps of "measuring" and "comparing" midkine levels, they clearly do not disclose "diagnosing the presence of early cancer, defined as stage 0 or stage I of the TNM classification, when the comparison of (b) indicates that the measured level is elevated as compared to the control level" as required by the claims as amended herein.

Regarding method claim 13 *et seq.*, Applicants again submit that Song *et al.* fail to disclose the use of midkine levels to determine the effectiveness of a particular treatment and/or a patient's prognosis. As noted previously, in order for serum levels of midkine to correlate to prognosis, there must be a direct relationship between measured midkine levels and a particular diagnosis (*e.g.*, stage of cancer, remission, survival rate, *etc.*). In this case, Song *et al.* expressly admit that they were unable to detect significant correlation between pathological features and serum midkine levels in certain carcinomas (see p. 377, col. 2). Furthermore, Song *et al.* fail to disclose or suggest a linear relationship between level of midkine and a particular prognosis or cancer stage. For example, differentiation describes the degree or extent that cancer cells resemble normal cells. Cancer cells that closely resemble the normal cells of the tissue they are derived from are termed "well-differentiated" while cancer cells that are primitive appearing or atypical in appearance are termed "poorly differentiated" or "undifferentiated". In many carcinomas, degree of differentiation is the most significant prognostic indicator for survival. However, Song's data in Table 1 fail to suggest any correlation between degree of differentiation and measured midkine levels. For example, whereas a sample from a patient with poorly differentiated lung carcinoma (case number 52) measured 450 pg/0.5 ml, a sample from a patient with well differentiated lung carcinoma (case number 55), who is presumably in better condition, with a better prognosis, displayed a higher midkine level of 720 pg/0.5 ml. Similarly, Song *et al.* disclose that the MK level associated with a well differentiated tumor that lacks node metastasis (case number 29 = 281

pg/0.5 ml) is twice that associated with a moderately differentiated tumor that is positive for lymph node metastasis (case number 33 = 146 pg/0.5 ml), a patient that, given the other measured factors, one would expect to have a more negative prognosis (*e.g.*, lower survival rate). Thus, one skilled in the art, upon reading the Song *et al.* reference, would not conclude that serum midkine levels can be correlated to cancer progression and prognosis as the pending claims require. Moreover, while the Song *et al.* reference discloses that serum levels of midkine may be "elevated" in certain carcinomas and, therefore, may distinguish the cancerous state from the normal state in such cases, there is no suggestion therein that specific, measured decreases in midkine levels correspond to a progression to a healthy state and/or a positive prognosis. Thus, Applicants respectfully submit that the Song *et al.* reference fails to anticipate or render obvious the invention of the pending claims.

Muramatsu et al.:

Claims 1, 4, 5, 8, and 9 stand rejected under 35 U.S.C. § 102(b) for being anticipated by Muramatsu *et al.* Claims 1, 4, 5, 8, 9, and 13 stand further rejected under 35 U.S.C. § 103(a) as being obvious in view by Muramatsu *et al.* According to the Examiner, Muramatsu *et al.* disclose a method of detecting early cancer and assessing MK gene expression. Specifically, the Examiner concludes that "[g]iven the endpoint of both methods are the same, comparing the level of human midkine protein between a cancerous sample and control sample, Muramatsu continues to anticipate the claims."

Applicants respectfully disagree and again submit that the Examiner is not considering elements of the claim, in particular the recitation of the preamble. Nevertheless, to expedite prosecution, Applicants have amended method claims 1 and 9 to include an affirmative recitation of "diagnosing the presence of" early cancer. While it may be argued that Muramatsu *et al.* disclose the steps of "measuring" and "comparing" midkine levels, they clearly do not disclose "diagnosing the presence of early cancer, defined as stage 0 or stage I of the TNM classification, when the comparison of (b) indicates that the measured level is elevated as compared to the control level" as required by the claims as amended herein.

On the issue of the obviousness of method claim 13 *et seq.*, the Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to implement a comparative analysis before and after a method of cancer treatment because a health practitioner would need to make a determination of whether the mode of treatment was indeed effective. However, while obviousness does not require absolute predictability, at least some degree of predictability is required. In this case, for serum MK levels to find reasonable utility in the assessment of cancer prognosis, one skilled in the art would need to be reasonably certain, *a priori*, that a direct, linear relationship existed between measured midkine levels and a particular diagnosis (*e.g.*, stage of cancer, remission, *etc.*). However, Muramatsu *et al.* simply disclose that midkine serum levels were slightly elevated in <u>*some*</u> of the hepatocellular carcinoma patients assayed as compared to levels in normal sera. There is absolutely no suggestion that serum midkine levels directly correlate with cancer progression and prognosis nor is there suggestion that specific, measured decreases in midkine levels correspond to a progression to a healthy state and/or a positive prognosis as required by the pending claims. In fact, Muramatsu *et al.* expressly state that "further studies are required to determine whether assaying of MK is helpful in the diagnosis or follow up of hepatocellular carcinoma." The conclusory statement that MK levels "might be" correlated with tumor grade is simply not an enabling disclosure of a direct relationship between MK levels and tumor prognosis, a relationship that necessarily must exist, *a priori*, for the proposed method to have a reasonable expectation of success. In order for a *prima facie* case of obviousness to be established, "[b]oth the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure," *In re* Dow Chem. Co., 837 F.2d 469,473; USPQ2d 1529, 1531 (Fed. Cir. 1988).

Given the fact that Muramatsu *et al.* provides no reasonable expectation of success, one skilled in the art would not have been motivated to utilize serum MK levels to assess cancer prognosis as presently claimed. Accordingly, Applicants respectfully submit that the Muramatsu *et al.* reference fails to render obvious the presently claimed invention.

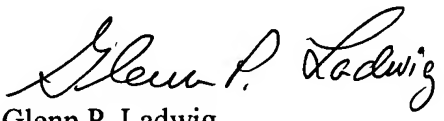
CONCLUSION

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of the issues in this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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GPL/mv
Attachments: Petition and Fee for Extension of Time
Appendix A (Kaname T. *et al.*)
Appendix B (Aridome, K. *et al.*)
Appendix C (Summary Chart)
Appendices D-M (Supporting documents)